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PHARMACOLOGY.—*Remedies for cyanide poisoning in sheep and cattle.*[1] A. B. Clawson, H. Bunyea, and James F. Couch, Bureau of Animal Industry.

The treatment of cyanide or prussic acid poisoning is an important problem to the veterinarian. Many cases of poisoning occur each year as a result of livestock feeding on cyanogenetic plants such as wild cherry, sorghum, arrow grass, and the like. Those plants that are capable of developing dangerous quantities of hydrocyanic acid under favorable circumstances are widely distributed and the problem of treating cyanide poisoning is not confined to a few localities, but is a matter of national interest.

Recent reports of the beneficial results following the use of new remedies in cases of this kind have provoked considerable interest as to their applicability to treatment under practical conditions. As most of the information available with respect to these remedies has been obtained from experiments on laboratory animals it was considered desirable to secure data concerning their effectiveness with larger animals. This paper reports the results obtained in the first two series of experiments in which sheep and bovines were the species used.

The experimental animals used had been kept under observation at the Experiment Station of the Bureau of Animal Industry, Bethesda, Md., for a sufficient period to establish knowledge of their healthy condition. Some of the animals had been used previously in other experiments, but at the time of these studies were normal. Except No. 1299, all of the sheep had been used in either anthrax or blackleg immunity tests and certain of the cows had been the objects of mastitis studies.

The remedies used had previously been the subject of studies by other workers in this field. Lang (8) in 1895 studied the antidotal

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action of sodium thiosulphate and other sulphur compounds in dogs and rabbits and found the first-named salt the most effective. His results showed that there is a great variation in effectiveness when the method of administration of the poison and antidote are varied. Hug (5), Turner and Hulpieu (11), and Forst (4) reported antidotal properties in sodium thiosulphate, but Hug considered it less effective than either methylene blue or sodium nitrite. The sodium thiosulphate used in our experiments was analytical reagent grade and was tested for identity and purity.

Methylene blue was found to be an antagonist of hydrocyanic acid in white mice by Sahlin (9) in 1926. Confirmation was obtained in the work of Eddy (3) on dogs and there has since been a large number of reports on the remedial value of that substance. Trautman (10) as a result of an extensive study of methylene blue as an antidote to gaseous hydrocyanic acid poisoning in mice, guinea pigs, and rabbits reports: "The average of results indicated no advantage in favor of the treated animals." Hug (5, p. 519) found methylene blue less effective than sodium nitrite. The methylene blue used in our experiments was the medicinal grade tested for identity and purity.

Sodium nitrite was proposed by Hug (5, p. 89) in 1932, who found it superior to methylene blue and sodium thiosulphate in dogs and rabbits. This salt has been used with considerable success in experimental cyanide poisoning of sheep and cattle by Fitch and his co-workers (personal communication) in Minnesota. Hug and Wendel (12) independently conclude that the mode of action of sodium nitrite is to convert part of the hemoglobin of the blood into methemoglobin, which then combines with the cyanide and forms a relatively non-toxic compound. In support of this hypothesis both investigators have demonstrated that methemoglobin itself acts as an antidote in cyanide poisoning. The sodium nitrite used in our study was of analytical reagent grade tested for identity and purity. The solutions used were freshly prepared for each experiment.

Sodium tetrathionate was found by Chistoni and Foresti (1) to protect against doses of potassium cyanide not much in excess of the m.l.d. Draize (2) found it more effective than methylene blue. The sample used by us was prepared according to the method of Klobukoff (7).

The use of a combination of sodium thiosulphate and sodium nitrite was suggested by the knowledge that these substances are thought to counteract the poisonous effects of cyanides in different ways, the nitrite through methemoglobin formation and the thiosulphate by converting the cyanide into thiocyanate. Since the quantity of hemoglobin that can safely be converted into methemoglobin for antidotal purposes is strictly limited by the minimal quantity of hemoglobin that is necessary to carry out the normal transportation of oxygen to the tissues, there is an upper limit to the dose of nitrite that can be administered with safety. Sodium thiosulphate, which does not convert hemoglobin into methemoglobin, and which does not react chemically with sodium nitrite, would serve to increase the effectiveness of the antidote without increasing its toxicity. After several experiments had been made on bovines and had demonstrated the superiority of the combination of remedies a paper by Hug (6, p. 711) was received in which, working with rabbits and dogs, he clearly demonstrated the effectiveness of the combination.[2]

For the purposes of the experiments reported in this paper the cyanide was given in the form of a freshly prepared solution of potassium cyanide. The specimen of salt used was of analytical reagent quality and analysis showed it to contain 98.12 per cent KCN. The cyanide was given by drench and the remedies given by intravenous or intraperitoneal injection except in two instances.

SYMPTOMS OF POTASSIUM CYANIDE POISONING

The symptoms of hydrocyanic acid poisoning have been described in various publications dealing with poisons, materia medica, and other subjects. The series of experiments carried out by the writers has furnished some detailed information regarding the sequence of the different symptoms, which it seems advisable to point out.

It is well known that an appreciable time elapses between the giving of potassium cyanide and the appearance of perceptible symptoms. In the cases which form the basis for this paper, this time did not differ particularly with the two classes of animals. For the cattle, the time varied from 0.5 minute to 2.5 minutes, and averaged 1.1 minutes. The longest time was for an animal given a small dose and which was given the material in the shortest time. With the sheep the time varied between 0.5 minute and 2 minutes, and averaged 1.5 minutes.

In the different experiments, from 0.5 minute to 2 minutes were required to give the drench. The elapsed time between giving of the

[2] Since this paper was prepared a report by CHEN, ROSE, and CLOWES (Proc. Soc. Exp. Biol. Med. 31: 250. 1933) has been received in which these authors show that the combination is very effective against potassium cyanide poisoning in dogs.

potassium cyanide and the appearance of symptoms was taken from the completion of the drenching.

In practically all cases the first indication of symptoms was an acceleration in rate and an increase in the depth of the respiration. In some instances, at the same time the animal appeared to be anxious as though apprehensive that something was not quite right.

In very mild cases, even when nothing was given to counteract the poison, the effect disappeared within a few minutes. Three poisoned cattle appeared to have entirely recovered within seven minutes after the cyanide was given. In two cases, a somewhat accelerated and unusually deep respiration and a somewhat increased pulse rate were all that were abnormal. The third cow, in addition, became very nervous, hypersensitive to movements, sounds, or other stimuli, and her pupils were considerably dilated. She also showed a slight leg weakness and appeared to be frightened. Two sheep, given small doses, apparently were entirely recovered in three and five minutes, respectively, after being given the cyanide. In the latter case, the pulse became very fast and there was slight spasmodic jerking of the muscles of the shoulders. The doses of hydrocyanic acid given these animals varied from 0.441 to 1.102 milligrams per kilogram of body weight. The smaller dose caused only a slight increase in the pulse rate of a cow.

When more seriously poisoned the rate and depth of the respiration rapidly increased and frequently culminated in spasms and dyspnoea. In one cow, spasms developed in nine minutes. In the other cattle spasms developed in five of the eleven cases and appeared in from 1.5 to 5 minutes, or an average of three minutes after the cyanide was given. With the exception of one case in which the notes are not definite, all the cases which did not have spasms were either light cases and recovered, or were given remedial treatment. In the one untreated fatal cattle case in which spasms developed, the spasms occurred at intervals for eleven minutes.

In the sheep, spasms of greater or less intensity developed in 22 of the 37 cases of poisoning. They occurred in from 1 to 14 minutes after the cyanide was given, or in an average time of $4\frac{1}{4}$ minutes. In some instances the duration was very short, consisting of a few spasmodic contractions. In some, they lasted for 7 to 9 minutes, while one animal had spasms which occurred at intervals for 51 minutes. Aside from two cases of the kind, the average duration was approximately $2\frac{1}{2}$ minutes.

The spasms varied considerably, some consisting of more or less violent kicking, and some opisthotonos, while in other cases there were violent tetanic contractions of the legs and body muscles, these usually being accompanied with jerky movements of the eye balls or rolling of the eye ball downward. At this stage, in the cattle cases, the jugular vein was very prominent and evidently engorged with blood. This, together with the blanching of the teats, would appear to indicate a contraction of the peripheral capillaries. During this period the venous blood was a bright red in color.

At approximately the same time that spasms developed, the respiration became labored or dyspnoeic and much slower than during the period of stimulation. As experimental treatments were given many of the poisoned animals during the period of spasms or very shortly thereafter, these animals can not be used in considering the progressive changes that occurred after that time. Only one untreated cow showed evidence of dyspnoea. This lasted for 43 minutes, or up to about two minutes before the animal died.

In six sheep which recovered, the period of dyspnoea lasted for from one to three minutes following which the respiration became easier and the animal gradually improved. In eight fatal cases, the dyspnoea lasted for from 11 to 38 minutes, or an average of 17 minutes. In other words, when dyspnoea continued for more than three minutes, the animals usually died. One sheep was an exception. On two occasions, this animal had several repeated periods of weakness, spasmodic muscular jerking, trembling and mild dyspnoea. These occurred during periods of 1 hour and 20 minutes on the first occasion and 1 hour on the second. The sheep recovered from both cases of poisoning.

During the period of dyspnoea the respiration varied greatly in rate. At times, it resembled panting, and at other times it was very deep, irregular and the expiration very much forced, while in other cases the animals were gasping for breath. In some cases it was more or less intermittent, being held for several seconds at a time. In mild cases the panting or labored respiration became less and less pronounced and then the animals passed into a recovery period. In fatal cases, it grew less deep and the periods between respiratory movements usually increased in length until the breathing ceased altogether. During this period the membranes were usually more or less cyanotic and the blood as seen in the eye veins, dark in color.

The period of dyspnoea was practically coincident with a severe weakness and depression, the animal being stretched out on one side. The eye reflex when noted was apparently normal and the animal usually kicked occasionally, or there was some trembling of the surface muscles. Considerable blood and watery liquid came from the nostrils and mouth of two of the cattle during this period. Both animals died.

The period of recovery in the two cattle given light doses was very short. Within 7 minutes in one case, and 10 minutes in another, after the cyanide was given, the animals appeared to have entirely recovered. Both were mild cases of poisoning. Some of the poisoned sheep recovered within a few minutes, while others were ill from 30 minutes to a few hours, depending on the severity of the poisoning. For all the sheep that recovered without the use of remedial treatment, the period of illness varied from four minutes to something more than $2\frac{1}{4}$ hours. The exact duration in the longer cases is not definitely known. In one fatal cattle case which did not receive any remedial measure, the animal was sick for 42 minutes. The sheep died after from 11 to 55 minutes of illness, the average time for the cases in which the notes are definite being 33 minutes.

LESIONS IN THE CATTLE

Autopsies were made on four of the five cattle that were fatally poisoned. None of the sheep were autopsied. In all the cattle the blood and the muscle tissues were very dark red in color. On being allowed to stand exposed to the air the blood, especially, soon became a bright red and resembled arterial blood. The lungs of one of the animals, No. 1267, were very severely congested and edematous. A considerably quantity of bloody and frothy liquid flowed from the mouth of this animal while it was in the latter stages of its illness. This apparently came from the lungs. The lungs of two of the other animals, Nos. 1264 and 1266, contained somewhat more blood than is usually present in normal cattle. This was not sufficient to call congestion however. Some bloody liquid flowed from the mouth of one of these animals, No. 1264, just before death. In the trachea of No. 1265, between the longitudinal folds of the mucosa, there were prominent hemorrhages which extended a short distance into the bronchial tubes. Petechiae were similarly present in the tracheal mucosa of No. 1267. This was the animal with the severely congested lungs. Aside from a few petechiae on the surface of the ventricles of No. 1264 and a slightly congested mucosa of the 4th stomach of No. 1267, the other tissues appeared to be normal.

TABLE 1.—Doses, Calculated as Hydrocyanic Acid, Given to Sheep and the Effects Produced when no Remedies were Used

Date	Animal No.	Dose given mg/kg and effect				
		No effect	Symptoms	Sick	Very sick	Death
1933 Oct. 3	1308					4.410
" 6	1315					3.307
" 10	1313					3.307
" 2	1303					2.646
" 2	1302					2.425
" 10	1310				2.425	
" 2	1307					2.315
" 2	1301					2.135
" 10	1313			2.315		
" 10	1300			2.315		
" 6	1310				2.205	
" 2	1300				2.205	
" 2	1306			2.205		
" 5	1310			2.092		
" 3	1312					1.764
" 5	1314		1.764			
" 6	1313		1.543			
" 5	1313		1.543			
" 3	1414		1.323			
" 5	1300		1.102			
Nov. 10	1299		0.992			
Oct. 3	1313	0.882				

TOXIC AND LETHAL DOSES OF HYDROCYANIC ACID FOR SHEEP AND CATTLE

In order to establish a basis on which to judge of the efficacy of remedial measures, various quantities of potassium cyanide were given and the subsequent effects allowed to take their natural course unmodified by remedies of any kind. The doses which were figured as milligrams of HCN per kilogram of the animal's body weight varied from 0.882 milligram to 4.41 milligrams per kilogram. The various doses as given to sheep are shown in Table 1, and those to cattle in Table 2. As shown in the tables the cases of poisoning were grouped into classes on the basis of the severity of the illness. The degree of illness is indicated by the terms "symptoms," "sick," "very sick," and "death." Among those classed as showing "symptoms" were included cases in which the respiration was distinctly stimulated and in which evidence of uneasiness or weakness developed. These animals were able to remain on their feet. The "sick" animals developed marked dyspnoea, and in some cases opisthotonos or mild spasms. They became too weak to stand throughout the illness, but did not lie stretched out on their sides. Those animals which went into a coma, developed pronounced spasms, or were lying stretched out on one side in a more or less comatose condition for some minutes are classed as "very sick."

The various doses given to sheep and the severity of illness of each case are shown in Table 1.

The results establish, fairly closely, the minimum toxic and lethal doses for sheep, when the cyanide is given as a drench and under the conditions accompanying these experiments. As symptoms were produced by 0.992 milligram per kilogram of animal weight calculated as hydrocyanic acid, and by all larger doses, and as 0.882 milligram was without apparent effect, 0.992 can be taken as close to the minimum toxic dose.

In one case, 1.764 milligrams per kilogram killed. In comparison the same dosage in another case produced only symptoms and in other cases sheep survived doses as high as 2.424 milligrams per kilogram. The small dose of 1.764 on the basis of other results appears erratic and may indicate an error. Two sheep were fatally poisoned by 2.315 milligrams per kilogram. Although one animal survived a slightly larger dose, the results in general appear to indicate that this figure is very close to the minimum lethal dose and for the purpose of this paper is so considered.

Although fewer of the experiments with cattle than with sheep furnish data regarding the degree of illness caused by different quantities of hydrocyanic acid, they furnish some evidence regarding the minimum toxic and the minimum lethal doses.

The smallest quantity which produced definite symptoms was 0.882 milligram per kilogram of animal weight. Following a dose of one half of this quantity or 0.441 milligram the pulse was somewhat accelerated. No other evidence of effect was noted and it was thought the pulse effect might be due in part at least to other causes. As the dose of 0.882 milligram caused very definite symptoms, consisting of accelerated pulse and respiration, nervousness, trembling and slight weakness, it would appear that for cattle the minimum toxic dose is somewhat less than 0.882 milligram, but more than one half this quantity.

A dose of 2.315 milligrams, or the minimum lethal dose for sheep, killed a cow and was thought by the observers to be somewhat more than would have been necessary to produce fatal results with the animal used in the experiment. In fact, one cow, not shown in Table 2, was made very ill on 2.042 milligrams and it was thought she would have died had remedial measures not been taken. Apparently the minimum letal dose then is close to the latter quantity. Both the minimum toxic and the minimum lethal doses appear to be slightly less for cattle than for sheep.

TABLE 2.—Doses, Calculated as Hydrocyanic Acid, Given to Cattle and the Severity of Illness Produced when no Remedy was Used

Date	Animal No.	Dose given mg/kg and severity of effect				
		Not sick	Symptoms	Sick	Very sick	Death
1933 Dec. 4	1267					2.315
Nov. 17	1265		1.021			
Nov. 28	1267		.992			
Nov. 28	1266		.882			
Nov. 28	1265	0.441				

REMEDIES USED AND THE RESULTS OBTAINED

As previously stated several substances have been used by various investigators to counteract the effects of hydrocyanic acid on animals.

TABLE 3.—Effects and other Data Regarding Substances used Experimentally in Treating Sheep and Cattle that were Poisoned by Hydrocyanic Acid.

Animal and designation	Date of experiment	Dose of HCN		Treatment			Minutes between giving HCN and giving remedy	Result
		Mg. per kg.	Times m.l.d.	Substance and strength of solution	Quantity given cc.	How given		
Sheep 1309	10– 3–33	3.307	1.42	Methylene blue 1 per cent	30	Intra-peritoneal	3	Death
Sheep 1313	10– 9–33	3.307	1.42	do	50	do	4.5	Recovery
Sheep 1300	10– 9–33	3.307	1.42	Sodium tetrathionate 10 per cent	10	Drench	At same time	do
Sheep 1305	10– 6–33	3.858	1.66	do	30 in 3 doses	Intra-peritoneal	5 to 1st dose 7 to 2nd dose $9\frac{1}{2}$ to 3d dose	Death
Sheep 1314	10– 6–33	3.307	1.42	do	20 in 2 doses	do	3.5 to 1st dose 4 to 2nd dose	do
Cattle 1264	11– 2–33	2.85	1.39	Sodium thiosulphate 10 per cent	20	Intravenous	6	Recovery
Sheep 1315	10– 3–33	3.307	1.42	do	10	Intra-peritoneal	2	do
Sheep 1310	10– 9–33	3.307	1.42	do	20	do	3	do
Sheep 1300	10– 9–33	3.858	1.62	do	20	do	3	do

Cattle 1263	9–28–33	2.042	1 ±	Sodium nitrite 10 per cent	20	Intravenous	10	Recovery
Do	9–29–33	3.063	1.5	do	20	do	21	Death
Sheep 1310	10– 3–33	3.307	1.42	do	20	Drench	0	Recovery
Sheep 1304	10– 2–33	3.307	1.42	do	10 in 2 doses	Intra-peritoneal	3 to 1st 6 to 2nd	do
Sheep 1305	10– 2–33	3.307	1.42	do	10	do	11	do
Sheep 1306	10– 6–33	3.858	1.66	do	10	do	10	Death
Sheep 1311	10– 3–33	4.410	1.9	do	20 in 2 doses	do	2 to 1st 25 to 2nd	do
Sheep 1304	10– 6–33	4.410	1.9	do	20 in 2 doses	do	8 to 1st 9 to 2nd	do
Cattle 1264	11–10–33	4	1.96	Sodium thiosulphate 20 per cent and sodium nitrite 20 per cent	10 10	Intravenous	4	Recovery
Cattle 1265	11–17–33	4.084	2	Sodium thiosulphate 20 per cent and sodium nitrite 20 per cent	10 10	do	4.5	do

TABLE 3 (Concluded)

Animal and designation	Date of experiment	Dose of HCN		Treatment			Minutes between giving HCN and giving remedy	Result
		Mg. per kg.	Times m.l.d.	Substance and strength of solution	Quantity given cc.	How given		
Cattle 1266	1– 8–34	5.105	2.54	Sodium thiosulphate 20 per cent and sodium nitrite 20 per cent	30 10	Intravenous	6.5	Death
Cattle 1265	12– 4–33	6.126	3	Sodium thiosulphate 20 per cent and sodium nitrite 20 per cent	10 10	do	3.5	do
Cattle 1264	11–17–33	8.168	4	Sodium thiosulphate 20 per cent and sodium nitrite 20 per cent	10 10	do	4	do

Two or more experiments were tried either singly or in combination, with each of the following: methylene blue, sodium thiosulphate, sodium tetrathionate, and sodium nitrite. Methylene blue was used with two sheep only. In each case it was given intraperitoneally. All remedies were given to cattle intravenously. The cyanide was administered as potassium cyanide.

It was desired to obtain information as to whether the remedies themselves acted by chemical transformation with the cyanide. Two sheep were given mixtures by mouth. One received a dose containing 1.42 m.l.d. of the cyanide mixed with 10 cc. of 10 per cent sodium tetrathionate solution and the second received a dose of 1.42 m.l.d. of cyanide mixed with 20 cc. of 10 per cent sodium nitrite solution. In both cases the animals became sick and exhibited typical early symptoms of cyanide poisoning. Both, however, soon showed improvement and recovered in a short time. The experiments indicated that the antidotal action of the remedies had taken place in the organism and that, therefore, the antidotal action is physiological. Had the remedy reacted completely with the cyanide *in vitro* the sheep would not have exhibited any symptoms of poisoning.

The substances used as remedies, together with the results and other data, are given in Table 3. In the opinion of the observers, several of the animals that died would probably have recovered if additional remedial measures had been used to support the experimental treatment.

Methylene blue

Two sheep, each given 3.307 milligrams of hydrocyanic acid per kilogram of body weight or 1.42 times the minimum lethal dose, were treated with intraperitoneal injection of a 1 per cent solution of methylene blue. One given 30 cc. 3 minutes after the prussic acid was given, and in the spasm stage of the illness, died. In this case it was not apparent that the illness was altered by the methylene blue. The second sheep was given 50 cc. of methylene blue solution intraperitoneally 4.5 minutes after the cyanide was administered and recovered. In these cases 50 cc. of 1 per cent methylene blue given intraperitoneally protected against 1.42 times the lethal dose. Three and one-half minutes after the methylene blue was given, the animal showed marked improvement and thirteen minutes later it got up.

Sodium tetrathionate

Of three sheep treated with sodium tetrathionate, one recovered and two died. The one which recovered was given a quantity of cyanide equivalent to 1.42 times the minimum lethal dose to which had been added 10 cc. of a 10 per cent solution of sodium tetrathionate. The two substances were mixed and given together as a drench. The sheep went through the early symptoms of hydrocyanic acid poisoning, but these did not reach the spasm stage. The illness was mild and within 13 minutes the sheep had completely recovered.

In one case 20 cc. of a 10 per cent solution of sodium tetrathionate given intraperitoneally failed to protect against 1.42 lethal doses of the cyanide and in another case 30 cc. failed to protect against 1.66 lethal doses. In one of these cases 3.5 minutes and in the other 5 minutes elapsed after the cyanide was given before the first injection of the remedy was administered. In these cases the sodium tetrathionate did not appear to be very effective as a remedy. Both animals had reached the spasm stage of illness and were prostrated when the tetrathionate was administered.

Sodium thiosulphate

This was tried experimentally with one cow and three sheep. Twenty cc. of a 10 per cent solution given intravenously to a cow 6 minutes after the cyanide was administered and 1.5 minutes after convulsions started protected the animal against 1.39 lethal doses. Improvement was noted in the animal's respiration within 1.5 minutes after the thiosulphate was given. One hour later the cow was looking bright and resting comfortably. She did not get to her feet for some hours later.

With one sheep 10 cc. and with another 20 cc. of a 10 per cent solution given intraperitoneally protected against 1.42 lethal doses when administered 2 and 3 minutes respectively after the cyanide was given. In a third case 20 cc. of the thiosulphate protected against 1.62 lethal doses. This was given 3 minutes after the acid was given. These three sheep were down on their sides and one of them, sheep 1310, was having spasms at the time.

Sodium thiosulphate under the condition of the experiment protected against 1.39 lethal doses of hydrocyanic acid in cattle and 1.62 lethal doses with sheep. It was, however, given during the early stages of the illness or before the evidences of respiratory paralysis became pronounced.

Sodium nitrite

Another substance used experimentally as an antidote for hydrocyanic acid poisoning was sodium nitrite. This, in a 10 per cent solution, was used intravenously on two poisoned cattle cases and as a drench or intraperitoneally with six sheep.

A cow given one lethal dose of cyanide recovered when given 20 cc. of a 10 per cent solution of the nitrite. In this case the nitrite was not given until ten minutes after the cyanide was administered or until the cow was down on her side and kicking spasmodically. The following day this animal was given 1.5 lethal doses of cyanide and 21 minutes later treated with 20 cc. of 10 per cent sodium nitrite solution given intravenously. At the time the nitrite was given she was prostrate on one side, the pulse was fast and beginning to grow weaker than it had been. No beneficial effect from the nitrite was noted. She died very shortly after the nitrite was administered.

One sheep given as a drench 1.42 lethal doses of cyanide to which was added 20 cc. of 10 per cent sodium nitrite developed the early symptoms of cyanide poisoning. The sheep became weak and went down on its side. She began to improve almost immediately and in 10 minutes after falling and 12 minutes after being drenched she had apparently almost completely recovered.

Two sheep given 1.42 lethal doses of cyanide and later given intraperitoneal injection of 10 per cent sodium nitrite recovered. In one case the nitrite was administered in two doses of 5 cc., one in 3 minutes or just after the sheep fell, and the second in 6 minutes after the cyanide was administered. The second sheep was treated with a single dose of 10 cc. of the nitrite solution. This was given 11 minutes after the sheep was drenched with cyanide, or 8 minutes after it went down on its side. At this time the paralytic effects of the cyanide on the respiration were beginning to be apparent.

When given ten minutes after 1.66 lethal doses of cyanide were administered 10 cc. of a 10 per cent solution of sodium nitrite failed to save the animal. Similarly 20 cc. of the nitrite failed to save two sheep that had been given 1.9 lethal doses each of cyanide even when the first half of the nitrite was administered shortly after the animal became ill. In one case 10 cc. was administered in 2 minutes and a second 10 cc. was given to the sheep in 25 minutes. In a second case the first 10 cc. was given in 8 minutes and the second 10 cc. in 9 minutes. Both sheep died.

Sodium thiosulphate and sodium nitrite combined

As sodium thiosulphate and sodium nitrite have different actions, both substances were administered to five poisoned cattle. In these cases 20 per cent solutions were used, one being administered immediately after the other. They were given intravenously. In two cattle, when these were administered within 4 and 4.5 minutes after the cyanide was given, the two substances protected against 1.96 and 2 lethal doses of the cyanide. In two other cases, similar doses of the thiosulphate and nitrite failed to protect against 3 and 4 lethal doses of the cyanide when 3.5 and 4 minutes respectively were allowed to elapse between the giving of the cyanide and the administering of the experimental remedy.

Similarly 10 cc. of sodium nitrite and 30 cc. of sodium thiosulphate did not prevent the death of a cow that had received 2.54 lethal doses of cyanide 6.5 minutes previously to the administering of the experimental remedy. In other words, by giving intravenous injections of sodium thiosulphate and sodium nitrite it was found possible to save cows poisoned by as much as 2 lethal doses of cyanide, but not when 2.54 lethal doses or more had been given.

SUMMARY

Experiments with sheep and cattle were made to determine the relative efficiency, under practical conditions, of four substances that have been suggested as remedies for cyanide poisoning. The substances used were methylene blue, sodium tetrathionate, sodium thiosulphate, sodium nitrite, and a combination of the two latter.

The animals were given drenches of potassium cyanide in water and the remedies were given at various times after the cyanide was administered. Except for two sheep for which the remedy was mixed with the cyanide and administered as a drench, the remedies were injected intraperitoneally and in the cattle they were injected into the jugular vein. All of the substances tried, offered some protection against the poisonous action of the cyanide.

The minimum lethal dose of hydrocyanic acid, administered as potassium cyanide in a drench, was determined to be; for sheep 2.315 mg. per kilo; for cattle nearly 2.042 mg. per kilo. The minimum toxic dose was found to be; for sheep 0.992 mg. per kilo; and for cattle somewhat less than 0.882 mg. per kilo.

In the experimental work with sheep 50 cc. of methylene blue protected against 1.42 lethal doses of cyanide, although 30 cc. failed to do so. Of the other remedies tried, sodium tetrathionate and sodium nitrite, each protected against 1.42 minimum lethal doses but failed to do so against slightly larger doses. Sodium thiosulphate protected against 1.62 minimum lethal doses. The combination of sodium thiosulphate and sodium nitrite was not tried with sheep.

In the cattle experiments, sodium nitrite protected against a single minimum lethal dose of cyanide but failed to do so when 1.5 minimum lethal doses had been given. Sodium thiosulphate protected against 1.39 minimum lethal doses. With cattle the best results were obtained with a combination of sodium nitrite and sodium thiosulphate which protected against 2 minimum lethal doses. Methylene blue and sodium tetrathionate were not used with poisoned cattle.

The results strongly indicate that in administering any of the substances tried as remedies it is of the utmost importance that they be given very promptly after symptoms of poisoning develop and before the period of respiratory paralysis sets in.

Aside from these remedies no other treatment was given the sick animals. It is our opinion based on our observations of the course of the sickness that in several cases additional treatment such as the stimulation of respiration and general supportive measures would possibly have altered the final result of the cases. It is suggested that, in cases of cyanide poisoning, treatment with the remedies used in this study could well be supplemented by other measures with better chances of success.

Two experiments indicate that the remedial action of nitrite and tetrathionate is physiological rather than chemical.

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CHEMISTRY.—*The pigment of the India red pummelo* (Citrus grandis *Osbeck*).[1] M. B. Matlack, Bureau of Chemistry and Soils. (Communicated by J. A. LeClerc.)

Through the courtesy of Dr. Walter T. Swingle of the Bureau of Plant Industry, the writer obtained three fruits of the India red pummelo from tree CPB 10058 of the Eustis Experiment Garden, Eustis, Florida. Since the pink grapefruit is a close relative of this fruit it was thought of interest to determine the nature of the pigment. Previ-

[1] Received May 21, 1934.